Multi-Center Sestamibi Parathyroid Imaging Study in Hawaii

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Technetium-99m (^{99m}Tc) sestamibi (MIBI) was first used as a parathyroid imaging agent in Hawaii in 1991. The purpose of this study was to determine the sensitivity and positive predictive value of the MIBI scan in detecting abnormal parathyroid glands. A retrospective, multi-center study from 1992-1994 involving 33 patients in four hospitals showed the overall sensitivity of the MIBI scan for detecting hyperparathyroid disease was 90%. The positive predictive value was 93%. It was more sensitive in detecting adenomas (95%) than hyperplasia (45%). In conclusion, the MIBI scan can be helpful in detecting abnormal parathyroid glands and may be most useful prior to reoperations for persistent and recurrent hyperparathyroidism.

Introduction

Clinical symptoms of hyperparathyroidism (HPT) are often nonspecific, especially early in the disease process. The incidence of HPT is increasing, with most patients found in an asymptomatic state by routine screening. The most common causes for this condition are parathyroid adenomas, hyperplasia, and rarely, neoplasms. In most cases, the cause of primary HPT is a solitary adenoma involving one of the parathyroid glands. For patients with end-stage renal disease (ESRD), the incidence of HPT is increased over that of the general public, and is almost always due to hyperplasia of the glands. Neoplasms in the parathyroids are rare, but do occur. A diagnosis of HPT can often be confirmed by elevated serum calcium levels and/or elevated parathyroid hormone levels. For patients with hyperfunctioning parathyroid glands, surgical exploration of the neck with removal of the suspicious gland(s) is the definitive treatment. This approach has been shown to be curative in the majority of cases, with surgical success rates of 90%-95%.[1]

Anatomically, parathyroid glands may be found anywhere from beneath the mandible to the level of the pericardium.[2] They are most commonly found anteriorly, in the lateral posterior surface of the lower pole of the thyroid, in the thymic tongue, or lateral to the lower pole of the thyroid.[3] Most individuals have four parathyroid glands, but there are documented cases of supernumerary glands. Ectopic glands have been located in the thyroid gland, substernal and mediastinal areas.

Due to variations in anatomical positions where the parathyroid glands have been found, and the concern that an abnormal number of glands may be causing the hypercalcemic condition, preoperative techniques that reliably locate the parathyroid glands have been sought after and investigated. A variety of imaging techniques have been attempted, including non-invasive tests such as ultrasound, magnetic resonance imaging, computed tomography, and nuclear medicine scans using a variety of radiotracers,[4,5] and the more invasive diagnostic tests such as venous sampling and selected arteriography. The search for valid and reliable methods has recently focused on the use of a radiotracer technetium-99m (^{99m}Tc) sestamibi. This radiotracer, originally marketed for cardiac imaging, has been shown to be useful in the preoperative detection and localization of parathyroid adenomas in patients having proven hyperparathyroidism.[5,6]

Available in Hawaii since 1991, the sestamibi (MIBI) scan is currently the most popular method used preoperatively to localize the parathyroid glands. During this study period, all four participating hospitals followed a similar procedure that included the use of a single radiotracer and a "washout" technique.[6] The purpose of this study was to determine the sensitivity, specificity, positive and negative predictive value of the MIBI scan by grouping the data from four local hospitals.

Methods

Institutional Review Board approval to conduct this medical record study was obtained from four hospitals in the metropolitan Honolulu area. These Hospitals were St. Francis Medical Center-Liliha, Queen's Medical Center, Kuakini Medical Center, and Straub Clinic and Hospitals, Inc. Due to the geographical proximity of these hospitals and the patient flow between them, a multi-center

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Fig. 1.—Sestamibi Scan Showing Prominant Left Lower Parathyroid Gland, Most Consistent with Parathyroid Adenoma (see arrow)

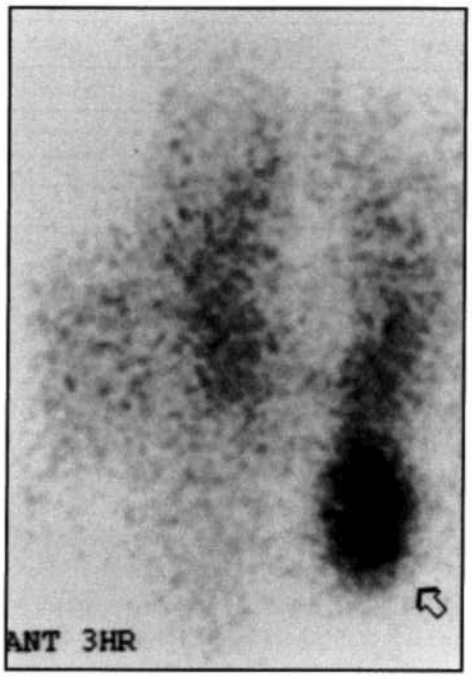

Table 1.—Mathematical Computation for Sensitivity, Specificity, Positive and Negative Predictive Value.

	Hyperparathyroid Disease		
MIBI Scan Results	Yes	No	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	

a = True Positives	b = False Positives	c = False Negatives	d = True Negatives

Sensitivity	$= \frac{a}{(a+c)}$
Specificity	$= \frac{d}{(b+d)}$
Positive Predictive Value	$= \frac{a}{(a+b)}$
Negative Predictive Value	$= \frac{d}{(c+d)}$

pooling of patients was used to obtain more comprehensive data. To identify study cases, the Nuclear Medicine Departments at the above institutions were contacted with a request for the names of individuals who had undergone a MIBI study of the parathyroid glands from 1992 to 1994. Using this patient list, inpatient medical records were reviewed from the respective hospitals.

When reviewing the medical records, if the patient had undergone a parathyroidectomy, the following information was obtained: pre-operative serum calcium level, surgical procedure performed, number and location of normal and abnormal parathyroid glands, time from incision to closure for the procedure, any surgical complications, pathology reports, and post-operative serum calcium level on the day of discharge. Patients who did not undergo surgery were excluded from the study.

If there was no inpatient medical record at the institution where the nuclear medicine study was performed, the referring physician's office was contacted and asked if the patient had undergone a parathyroidectomy at any other local hospital. Records were then reviewed at these hospitals.

Sestamibi Scan

A MIBI scan was performed when HPT was suspected. For this scan, no specific patient preparation is required. All four participating hospitals used similar, although not identical, imaging techniques as described by Taillefer[6] with early and late MIBI imaging. With the patient supine and neck extended, anterior images of the neck and chest were acquired 10-15 minutes and 2-3 hours after intravenous administration of 20-24 mCi MIBI. Analog images were acquired with a preset time of 10 minutes using a scintillation camera with low energy, high resolution or all-purpose parallel hole collimator. Digital data (128 X 128 matrix) were also acquired during 10 minutes. Optional views included imaging with a pinhole collimator. SPECT (tomography) or use of a second tracer was not utilized during the time interval for this study. The initial image obtained at 10-15 minutes after injection of MIBI was used as the "thyroid" phase of the study and represents the concentration of the tracer by the thyroid parenchyma. The second image performed between 2-3 hours after injection corresponded to the delayed or "parathyroid" phase. Both initial and delayed images of a given patient were placed side by side for comparison and viewed on either hardcopy or computer display.

A positive MIBI scan for parathyroid **adenoma** was defined as an area of increased focal uptake of the tracer in projection of the thyroid bed and surrounding areas or mediastinum which showed either a relative progressive increase over time[7] or a fixed uptake which persisted on delayed imaging (see figure 1). This pattern differs from uptake in the normal thyroid tissue which progressively decreases over time (differential washout analysis). This is due to the fact that the tissue kinetics of the thyroid and hyperactive parathyroid have substantially different resident times for Tc-99m sestamibi. The location of the parathyroid usually included the exact location of the parathyroid: right or left side; upper, lower or ectopic location. Parathyroid **hyperplasia** was interpreted only if more than one abnormal focus was identified on dual-phase MIBI imaging.

Data Analysis

For each patient in this study, the results of the MIBI scan from the nuclear medicine report, the surgical report and pathology findings were retrospectively compared to determine the sensitivity and specificity of the MIBI scan. For a true positive, the scan interpretation was the same as the surgical and pathology findings. A false positive study was when the MIBI scan determined disease, but the diagnosis did not match the surgical findings, or there was no parathyroid disease. A false negative study did not show any abnormality on the scan, while the surgical and pathological reports showed abnormally enlarged tissue. False negative results were also

Table 2.—Patient Diagnosis Comparing Sestamibi Scan Results & Actual Surgical/Pathology Results.

	Actual Surgical Pathology Results		
MIBI Scan Results	Adenoma	Hyperplasia	Normal
Adenoma	n = 19	n = 4	n = 2
Hyperplasia	n = 0	n = 5	n = 0
Normal	n = 1	n = 2	n = 0

	True Positive	True Negative	False Positive	False Negative
Adenoma	19	0	6	1
Hyperplasia	5	0	0	6

Sensitivity for Adenoma	19/20	95%
Positive Predictive Value	19/25	76%
Sensitivity for Hyperplasia	5/11	45%
Positive Predictive Value	5/5	100%

assigned to patients where one type of disease was diagnosed by MIBI and another type was diagnosed by pathology.

Sensitivity was defined as the number of true positives divided by the sum of true positives and false negatives. Specificity was defined as the number of true negatives divided by the sum of true negatives and false positives. The positive predictive value (PPV) of the MIBI scan was calculated by dividing the number of true positives by the sum of true positives and false positives. Negative predictive value (NPV) was the number of true negatives divided by the sum of false negatives and true negatives (Table 1).

Results

A total of 48 patient names were obtained from the Nuclear Medicine Departments of the four participating hospitals. Of these 48 patients, 33 underwent surgery on their parathyroid glands, and the data analysis refers only to this group. There were 22 females (67%) and 11 (33%) males. Average age of patients during the time of the scan was 50.6 years old (range 21 to 86). Average time from scan to surgery was 2.2 months (range 1 day to 18 months). Preoperative serum calcium levels ranged from 9.5 to 12.9 mg/dl (mean of 11.2 ± 0.78 mg/dl). Three patients had undergone previous neck exploration. Eight of the patients has a primary diagnosis of end-stage renal disease and secondary HPT; 25 of the patients had primary HPT.

MIBI scans preoperatively diagnosed 25 patients with adenomas and 5 patients with hyperplasia. Three scans were interpreted as normal. In contrast, operative and pathologic findings confirmed 20 cases of adenoma and 11 cases of hyperplasia. Two cases were negative for parathyroid disease and resulted in thyroid biopsy or thyroid goiter removal. In the 3 cases where the MIBI scan was read as normal, the operative and pathologic findings were positive for adenoma (1 case) or hyperplasia (2 cases). In 4 cases, the MIBI scan was positive for parathyroid adenoma, but surgical findings were positive for hyperplasia (Table 2).

Table 3.—Patient Diagnosis Comparing MIBI Scan Results & Actual Surgical Confirmation of Disease

	Surgical Confirmation of Parathyroid Disease	
MIBI Scan Results	Positive	Negative
Positive	n = 28	n = 2
Negative	n = 3	n = 0

Sensitivity	28/31	90%
Specificity	unable to determine due to no true negatives	
Positive Predictive Value	28/30	93%
Negative Predictive Value	unable to determine due to no true negatives	

Three patients had a history of previous neck surgery. One of these patients had persistent hyperplasia following near-total parathyroid gland resection for hyperplasia that had occurred 3 years earlier. The MIBI scan and surgical/pathology results both diagnosed hyperplasia. Another patient who was diagnosed with hyperplasia in surgery had previously undergone a thyroid lobectomy. This patient had preoperative MIBI scans which were interpreted as adenoma initially, followed by compensatory hypertrophy. The last case involved resection of a Wharton's Tumor six months prior to the MIBI scan. This scan was interpreted as adenoma, but at surgery only 3 normal parathyroid glands were found.

Overall, the sensitivity of the MIBI scan for HPT disease (not differentiating adenoma from hyperplasia) was 90%. The positive predictive value (PPV) was 93% (Table 3). Specificity or negative predictive value (NPV) based on presence of disease could not be determined because no true negatives were identified by the study's methodology.

When the results were separated into categories of adenoma and hyperplasia, the sensitivity and PPV changed. The sensitivity of the MIBI scan for adenoma was 95% (19/20 cases), with a positive predictive value of 76% (19/25 cases). The sensitivity of the MIBI scan for hyperplasia was 45% (5/11 cases), with a PPV of 100% (5/5 cases), as shown in Table 2. For all cases, the specificity and NPV were not determined due to the lack of true negatives (i.e. not all patients with negative scans underwent surgery to confirm normality).

There were 3 cases where the MIBI scan was interpreted as normal, but parathyroid disease was confirmed by pathology. In 1 case, an adenoma was found, and in 2 cases, hyperplasia was found. In 4 cases, hyperplastic parathyroid disease was found at surgery, but incorrectly identified as adenoma by preoperative MIBI scans. In the calculations for sensitivity and PPV, these cases were used both as false positive for adenoma and false negative for hyperplasia.

The gland weight of the diseased parathyroids was listed for 28 of the 33 patients. The average gland size of a parathyroid adenoma was 1.45 ±1.2 gms (range 0.2 to 4.98 gms, n=18 glands in 18 patients). Hyperplastic glands averaged .55 ± .48 gms (range 0.02 to 1.9 gms, n=34 glands in 10 patients). The difference in gland weight was significant (p=.008, 2-tailed t-test).

The sensitivity, specificity, positive and negative predictive value based on individual glands can be calculated from this data, and are

Table 4.—Comparison of MIBI Scan Results & Actual Pathology Results by Individual Gland			
	Pathology Results		
MIBI Scan Results	Adenoma	Hyperplasia	Normal*
Adenoma	16	4	5
Hyperplasia	0	18	0
Normal	4	18	19

* also includes 2 cases of thyroid disease

	True Positive	True Negative	False Positive	False Negative
Adenoma	16	19	9	4
Hyperplasia	18	19	0	22

shown in Table 4. Although no individuals with normal scans underwent an operation, glands that were normal on MIBI scan were biopsied in some cases, and were used as true negatives if the MIBI report and pathology report were both interpreted as normal.

Postoperative serum calcium ranged from 7.8-11.4 mg/dl (mean 9.09 ± 0.92 mg/dl). Postoperative complications included 7 cases of hypocalcemia and one case of hoarseness and difficulty swallowing. All complications resolved by the time of discharge. There were no reoperations or recurrences noted during this study period.

Discussion

The sensitivity of the MIBI scan has been shown to be equal or superior to other forms of preoperative imaging of the parathyroid glands. There are multiple ways this radiotracer is used: as a single radiotracer in a washout technique as described,[6] in combination with other radiotracers in subtraction studies[4,8,9,10,11,12,13,] with intraoperative PTH measurement,[14] with factor analysis of dynamic structures,[15] and intraoperatively combined with nuclear medicine imaging.[16] Review of these studies demonstrate a sensitivity range of 84%-100% for imaging parathyroid adenomas and 55%-100% for detecting hyperplasia.

The overall sensitivity of the MIBI scan for diagnosing hyperparathyroid disease was 90% in this study. This supports the national literature that the MIBI scan was more sensitive in diagnosing adenoma (95%) than hyperplasia (45%).

Assignment to categories in this study was strict as reflected in the sensitivity and specificity. A match between the correct anatomical position on both MIBI scan and surgical/pathology reports was required for a true positive reading in Table 3. In all cases, the correct side of the neck was identified, but there were 6 cases where there was a difference between quadrant named on scan and surgical/pathology location of diseased gland. True negatives were only assigned to pathologically normal glands and this sample was limited. Unfortunately, the study team was unable to determine the specificity and NPV in the study as it was designed. There was an inherent bias because the patients studied presumably had chemical HPT and were scheduled for surgery (or biopsy) because of symptomatology. The specificity in the literature for scintigraphy using any method in patients without HPT has been reported in the range of 77-100%.[5]

As noted in other studies, the sensitivity for detecting adenomas was much higher than for hyperplasia. While the MIBI scans were accurate in picking up disease, they were not as accurate in differentiating adenoma from hyperplasia. The difference in gland size may be a factor. The most obvious hazard in this scenario is that the neck exploration will be stopped after the abnormal gland(s) identified by scan is removed, leaving behind unsuspected hyperplastic glands that will need to be removed at subsequent surgery.

A proposed benefit to preoperative scanning is a decrease in operative time.[8] If the scan clearly documents a single adenoma, the opposite side may not need to be explored. This benefit, however, has not been universally supported.[1] In this study, the mean operating time from incision to skin closure was 107.7 ± 33.9 minutes (range 56-185 minutes). A comparison group of patients who had parathyroid surgery without preoperative MIBI imaging was not drawn due to the different number of surgeons performing the operations and the multiple hospitals that were involved in this study. Thus, whether preoperative imaging can actually decrease operative time could not be validated from this study data.

Finally, there is controversy over the routine use of the MIBI scan, debating the benefits to the patient and surgeon versus the expense of the test, and the true surgical advantage provided by its use preoperatively. A quote frequently used in this debate is that "the only localization needed prior to surgery is to locate an experienced parathyroid surgeon."[5,14] Whether these localization tests should be used in all patients, or reserved for those undergoing repeated exploration is currently being debated. One side recommends the use of this scan as a preoperative exam only in cases of reoperation for persistent or recurring hyperparathyroidism,[1,5,6,11] while others feel that preoperative localization in initial neck operations is useful.[10] Concurrent with the debate over patient selection are many issues regarding technique, to include the optimum imaging protocol, radiotracers used alone or in combination, and time frames from dosing to imaging.

Summary

Sestamibi parathyroid imaging is relatively new, but seems to be a significant improvement over previously reported scintographic techniques. In our local experience, it has a 90% sensitivity in detecting an abnormal (enlarged) parathyroid gland, but is less reliable in actually differentiating an adenoma from hyperplasia. The local experience in Hawaii confirms published data. Sestamibi scans overestimates adenoma (sensitivity 95%, PPV 76%) and underestimates hyperplasia (sensitivity 45%, PPV 100%). There were two false positives and three false negatives for HPT (in the literature, false positives tend to occur with thyroid nodules and false negatives with smaller glands of hyperplasia).[5] Of the 33 patients in our study, 25 had primary HPT and 8 had secondary HPT with ESRD. A small subpopulation of 3 patients had previous thyroid or parathyroid surgery. No ectopic glands occurred in this study. Adenoma could not be reliably differentiated from hyperplasia in the study population.

Despite the excellent results of the MIBI scan, it is unclear and still controversial whether this accuracy can compete with the even

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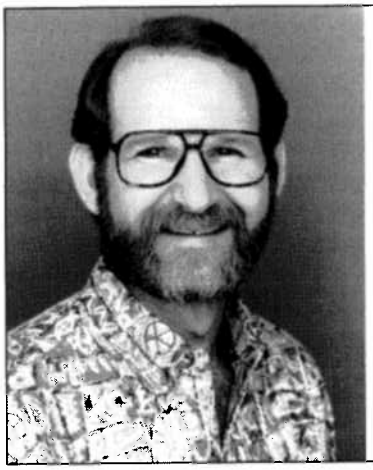

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better success of an experienced surgeon in initial surgeries for HPT. Some argue preoperative localization for HPT is probably not justified. There may, however, be a role for preoperative localization in patients with recurrent HPT and previous parathyroid or thyroid neck surgery. Controversy aside, MIBI scan in most cases may still be the best technique in nuclear medicine for detecting abnormal parathyroid glands.

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